REMARKS

Claims 16-43 are pending herein. By this Amendment, 1-15 are canceled, without prejudice or disclaimer, and new Claims 16-43 are added.

Support for the new claims is found in the specification at, *inter alia*, paragraphs [0016]-[0017], [0025], [0027]-[0028], [0030]-[0036], [0039]-[0046], [0049]-[0052], [0058]-[0060], [0133], [0143], [0173]-[0182], and [0209]-[0219]. Paragraph numbers correspond to the published application, US 2005/0158372 A1. No new matter is added by this Amendment.

In addition, a Substitute Sequence Listing is filed concurrently herewith and is supported by paragraphs [00125]-[0126] and [0210]-[0211].

I. SUMMARY OF EXAMINER INTERVIEW

Applicants thank Examiner Calamita and Primary Examiner Strzelecka for the courtesies extended to them and to their representative at the June 12, 2007 personal interview.

Applicants and Applicants' representative maintained that one of ordinary skill in the art would not have been motivated to combine the teachings of Wu et al. and Singh et al. In particular, Wu et al. requires DNA-antibody conjugates. Applicants' representative argued that any combination of Wu et al. and Singh et al. would require such DNA-antibody conjugates and therefore would also result in encapsulating the antibody or result in nucleic acid sequences outside the liposome. Examiner Calamita asserted that she was relying on Wu et al. for teaching a DNA "marker".

Applicants argued that nucleic acid sequences cannot be encapsulated in a lipid as disclosed in Singh et al. At the interview, Applicants pointed to many advantages of the present invention, for example, the ability to sequester nucleic acid sequences and to degrade background DNA or RNA.

II. STANDARD FOR OBVIOUSNESS

In the *KSR* case, the Supreme Court reiterated that the framework for applying the statutory language of 35 U.S.C. 103 was set out in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966):

> the scope and content of the prior art are to be determined; differences between the prior art and the claims in issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the subject matter sought to be patented.

KSR Int'l v. Teleflex Inc. (U.S. 2007). Although the Supreme Court held that the Teaching, Suggestion, Motivation (TSM) test is not the flexible test required by *Graham*, the Court noted that rejections based on obviousness grounds cannot be sustained by mere conclusory statements.

The Supreme Court stated that a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way that the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what is already known. By asserting that a claimed combination is obvious to try, there should be demonstrated both (1) a design need or market pressure to solve a problem and (2) a finite number of identified, predictable solutions.

II. REJECTION UNDER 35 U.S.C. 103(a)

Claims 4-14 were rejected under 35 U.S.C. 103(a) over Singh et al. (Anal. Chem., 2000) in view of Wu et al. (Letters in Applied Microbiology, 2001). Claims 4-14 are canceled. This rejection is respectfully traversed with respect to the new claims.

A. Singh et al. Does Not Teach or Suggest Encapsulation of Nucleic Acid Segments

Singh et al. discloses using liposomes containing gangliosides as probes for detecting bacterial toxins. To impart signal generation capability to the liposomes, fluorophore-labeled lipids (rhodamine-labeled lipid) are incorporated into the bilayer of the liposomes. The fluorescent liposomes were used in sandwich fluoroimmunoassays for tetanus, botulinum, and cholera toxins and as low as 1 nM of each toxin could be detected (page 6019, left hand column). The signal molecules (i.e. rhodamine-labeled lipids) may be encapsulated, although leakage upon storage is a serious concern (page 6020, right hand column).

Singh et al. does not teach or suggest encapsulating a plurality of identical nucleic acid segments within closed shell liposomal bilayers.

B. Wu et al. Requires DNA-Antibody Conjugates and Does Not Teach or Suggest Use DNA Markers Alone

Wu et al. does not overcome the deficiencies of Singh et al. Wu et al. discloses using immuno-PCR to develop a sensitive assay to detect botulinum neurotoxin type A antigen (page 32). DNA-antibody conjugates are formed by the direct covalent attachment of a DNA amplification substrate to an antibody of interest.

Wu et al. indeed teaches a reporter DNA molecule (marker) amplified by PCR, as asserted by the Examiner. However, the Wu et al. explicitly teach and require reporter DNA covalently linked to antibodies through amine and sulphhydryl groups.

As discussed at the interview, Singh et al. and Wu et al. cannot be combined because any such combination would result not only in the encapsulation of the DNA reporters, but also encapsulation of the antibodies because Wu et al. requires DNA-antibody conjugates. This would render the process of Singh et al. inoperable as the encapsulated antibodies would therefore be unable to capture any antigen/toxin. It is axiomatic that a proposed modification cannot render the prior art inoperable for its intended purpose. See MPEP 2143.01(V).

Moreover, there is no recognition or appreciation that the combination of Wu et al. and Singh et al. could possibly lead to a lower detection limit than already disclosed in Wu et al. (3.33×10^{-17} mol). A 1000-fold improvement of the minimum detectable concentration of Singh et al. (10^{-9}) would be on the order of 10^{-12}, not the sub-attomolar level (10^{-18}) of the claimed invention.

C. The Standard for Obviousness Has Not Been Met

As stated in *KSR*, a patent application composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art. However, this is what the Examiner has done by selectively extracting one element disclosed in a reference (e.g., DNA reporter) and combining it with another element of a different reference (e.g., liposome). Nothing has been shown which evidences (1) a design need or market pressure to solve a problem and (2) a finite number of identified, predictable solutions.

First, the only advantage or expected benefit disclosed is Wu et al. is that using DNA-antibody conjugates results in a 1000-fold enhancement in detection sensitivity

over "conventional enzyme-linked immunosorbent assays". Wu et al. does not teach or suggest using DNA markers alone in other kinds of assays unlinked from antibodies. Further, no problems with the assays of Singh et al. have been identified.

Second, there has been no reasoning provided as to why one of ordinary skill in the art would have identified or predicted that nucleic acid segments could even be encapsulated in lipid bilayers. According to *KSR*, there must be a finite number of "identified, predictable solutions" to solve a problem which would support a combination of elements. Importantly, during the personal interview, two persons skilled in the art (the Applicants) stated that one of ordinary skill in the art would not have been prompted to combine the nucleic acid segments and liposomal bilayers in the way the claimed invention does.

At the interview, the Examiners indicated that there were references other than Wu et al. which teach the use of DNA markers by themselves without covalent attachment to antibodies. No such references have been applied against the claims.

D. Secondary Considerations Must Be Considered

As required by *KSR* and *Graham*, secondary considerations must be considered. However, there has been no acknowledgment or consideration of the secondary considerations as shown by Exhibits 1-6 attached to the Response filed on January 2, 2007, which clearly evidenced solution to unsolved needs, for example:

> Previous attempts to couple antibodies and PCR often led to incorrect results due to contamination for the lab or instruments involved . . . The new test is quick and as much as **1,000 more times sensitive in detecting cholera or botulin than any other assay**, according to the paper presented the research in yesterday's *Nature Biotechnology*.

(ScientificAmerican.com, emphasis added).

> The technique demonstrated **exceptional sensitivity**, with a detection threshold of 10 toxin molecules in a 150 µL sample.

(chemistry.org, emphasis added).

For all these reasons, it would not have been obvious for one of ordinary skill in the art to practice the claimed methods in view of the combined teachings of Singh et al. and Wu et al. Reconsideration and withdrawal of the rejection are respectfully requested.

IV. CONCLUSION

In view of the remarks above, Applicants respectfully submit that the present application is in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,

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